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SIRT1 Activities Ameliorate High Glucose Induced Endothelial Cellular Damage and Dysfunction of eNOS in an AMPK-Dependent Manner

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OBJECTIVES SIRT1 is a class III histone deacetylase thought to regulate cellular metabolic pathways in response to alterations in vascular complications of diabetes This study was aimed to investigate its regulation on high glucose-induced damage and dysfunction in human umbilical vein endothelial cells (HUVECs) involved in AMPK/eNOS signaling.

METHODS HUVECs were cultured in medium with normal glucose (NG), high glucose (HG) and HG + Resveratrol (the natural SIRT1 activator, 1-10 μM). Cell viability and nitric oxide (NO) production were measured by MTT or NO testing kits respectively. The protein expression of SIRT1, eNOS, AMP-activated protein kinase (AMPK), Akt and Ca(2+)/calmodulin-dependent protein kinase II were examined by Western blotting.

RESULTS Administration of Resveratrol dose dependently prevented HG-induced impairment of cell viability and NO production in HUVECs. The decrease of SIRT1 expression induced by HG was restored by Resveratrol treatment. Resveratrol also rescued HG-induced decrease of eNOS phosphorylation at Ser-1177 and Ser-633. Inhibition of AMPK by compound C or knockdown of $AMPK_{\alpha1/2}$, but not Akt or Ca(2+)/calmodulin-dependent protein kinase II, abolished the protective effect of Resveratrol on eNOS phosphorylation at Ser-1177. The protective effect of Resveratrol on eNOS phosphorylation at Ser-633 was also abolished by inhibition of AMPK but not by Akt.

CONCLUSIONS Our results provide for the first evidence that SIRT1 activities ameliorate HG-induced cell damage and eNOS dysfunction in an AMPK-dependent manner in HUVECs, and suggest that SIRT1 may be a potential therapeutic target for vascular complications in diabetes.

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Uric Acid is Positively Associated with hypertension But Negatively Associated With Coronary Artery Disease in Postmenopausal Women: The Multi-Ethnic Study of Atherosclerosis

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OBJECTIVES The relationships between uric acid with hypertension and or coronary artery disease, as well as the gender differences in these relationships are controversial. We investigate the association between uric acid with hypertension and or coronary artery disease in the Han, Uygur, and Kazakh in Xinjiang in western China.

METHODS The study Medical check-up data from 6,064 Han 1,844 Uygur and 445 Kazakh population were examined. The prevalence of hypertension and coronary artery disease was calculated by the quartiles of serum levels of uric acid. Correlation co-efficient between hypertension and coronary artery disease related risk factors were calculated and compared between men and women, especially postmenopausal women.

RESULTS The mean levels of mean uric acid were significantly higher in men than in women. The serum uric acid level was significantly higher in postmenopausal women than in without postmenopausal women (4.64±1.11 vs 4.24±1.03 mg/dl, P <0.001). The logistic regression analysis showed that Uygur women [OR=1.39, 95%CI (1.08-1.78), P = 0.01] compared with Han women have 1.39 risk for have coronary artery disease; the subjects of BMI [OR=1.08, 95%CI (1.06-1.11), P<0.01]; and eGFR<60 vs.≥60 [OR=1.22, 95%CI (1.01-1.46), P =0.04] were the independent risk factor for Hypertension women; the subjects of Age and Diabetes were the independent risk factors for the participants with CAD and or Hypertension; [OR=1.07, 95%CI (1.06-1.09); P <0.01] vs. [OR=1.04, 95%CI (1.03-1.05), P <0.01] and [OR=2.27, 95%CI (1.74-2.98), P <0.01] vs. [OR=2.24, 95%CI (1.74-2.89), P <0.01]. Although the SUA Q4 quartiles is the risk factor for hypertension but negatively for women with coronary artery diseases, [OR=1.17, 95%CI (0.87-1.59), P =0.3; vs. OR=1.34, 95%CI (1.00-1.84), P =0.048]. An increased risk for Hypertension in the highest quartile SUA was higher in postmenopausal women. Comparing the highest to the lowest quartile, OR were 1.417 (95% CI, 0.972 to 2.067, p=0.07) and OR were 0.99 (95% CI, 0.641 to 1.53, P =0.965), respectively.

CONCLUSIONS The serum uric acid there is a significant association between SUA and Hypertension in women, postmenopausal women but negatively association between SUA and CAD in women, postmenopausal women. Furthermore, we found the risk of Hypertension to be higher in postmenopausal women than in not-postmenopausal women in the highest quartile of the SUA group, and the risk of CAD was not having statistical significance. We should pay more attention about women, especially postmenopausal women with hypertension.

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Noninvasive Vagus Nerve Stimulation Breaks the Vicious Cycles between Connexin Dysfunction and Early Atrial Electrical Remodeling

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OBJECTIVES We previously showed that low-level tragus nerve stimulation (LL-TS) effectively reduced atrial fibrillation (AF) duration closely associated with atrial connexins (Cxs) expression. Herein, we will further study the role of Cxs in the early atrial electrical remodeling induced by rapid atrial pacing (RAP).

METHODS Nineteen beagle dogs were randomly divided into 3 groups. RAP group (n = 6): RAP was performed at left atrial appendage for 9 hours. LL-TS group (n = 7): RAP with LL-TS treatment lasted for 9 hours. Sham group (n = 6) underwent sham RAP and LL-TS. Tragus nerve stimulation (20Hz, 1ms) was delivered to the right tragus in external auditory canal with ear-clips connected to a custom-made stimulator. The voltage slowing sinus rate was used as the threshold for setting LL-TS at 80% below that. After multi-electrode catheters were attached to atrial and all PV sites, electrophysiological parameters were detected. At the end of protocol, Western blotting, immunohistochemical staining and real-time polymerase chain reaction were performed for Cx40 and Cx43 measurements in isolated atrial tissues.

RESULTS After 9-hour RAP, the effective refractory period (ERP) progressively shortened and ERP dispersion and window of vulnerability progressively (WOV) increased, which were also associated with down-regulation and abnormal distribution of both Cx40 and Cx43 in RAP group when compared to sham group ($P < 0.05$). With LL-TS after treatment, ERP reduction, ERP dispersion and WOV increase returned to baseline ($P < 0.05$). Simultaneously, the loss of atrial Cx40 and Cx43 were prevented by LL-TS ($P < 0.01$).

CONCLUSIONS RAP induces atrial electrical remodeling and connexins remodeling, which may form a vicious cycle and may perpetuate each other. LL-TS could reverse these two remodeling and potentially break the vicious cycles of “AF begets AF”.

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NADPH Oxidase-Dependent NLRP3 Inflammasome Activation and its Important Role in Diabetic cardiomyopathy

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OBJECTIVES Diabetes mellitus is strongly associated with cardiomyopathy. The underlying mechanisms for the development of diabetic cardiomyopathy (DCM) are complex and not completely understood. Oxidative stress plays a key role in the pathogenesis of DCM. Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome is associated with metabolic disorder and cell death, which are important triggers in diabetic cardiomyopathy. We aimed to explore whether NADPH Oxidase-Dependent NLRP3 Inflammasome Activation contributes to DCM.

METHODS A high-fat diet and low-dose streptozotocin administration were used to induce type 2 diabetes in Wister rats. Diabetic rats were treated with NADPH Oxidase Inhibitor (apocynin,$0.2g \cdot kg^{-1} \cdot d^{-1}$) TSG